Remarks

The Office Action mailed 21 January 2004 has been received and reviewed. Claims 1, 2, 8, and 15 having been amended, the pending claims are claims 1-41. Claims 8-14 and 24-41 being withdrawn from examination as drawn to non-elected inventions, the claims currently under examination are 1-7 and 15-23. Reconsideration and withdrawal of the rejections are respectfully requested.

AFFIRMATION OF PROVISIONAL ELECTION

The Examiner issued a Restriction Requirement under 35 U.S.C. 121 in the above-identified application, grouping the claims as follows: Group I, Claims 1-7 and 15-23 drawn to a method of determining whether an individual has or is at risk for developing Usher syndrome Type IIa; Group II, Claims 8-14 drawn to a method for detecting the presence or absence of an usherin protein; Group III, Claims 24-29 and 38-41 drawn to a test kit for detecting the presence or absence of Usher syndrome Type IIa in an individual comprising an antibody and a detectably labeled usherin protein; and Group IV, Claims 30-41, drawn to a test kit for detecting the presence or absence of Usher syndrome Type IIa in an individual comprising a first antibody that immunoreacts with usherin protein and a second antibody that immunoreacts with a portion of human usherin protein.

A provisional election to prosecute claims 1-7 and 15-23, Group I, was made in response to a telephone conversation with the Examiner on 17 December 2003. The provisional election to prosecute Group I is herein affirmed with traverse.

The Restriction Requirement is traversed on the basis that the claims of elected Group I and non-elected Group II are so interrelated that the inventions as claimed can be readily evaluated without placing an undue burden on the Examiner. The claims of both Group I (claims 1-7 and 15-23) and Group II (claims 8-14) are all drawn to a "method comprising: obtaining a biological sample from the individual; incubating the biological sample with at least one antibody which is immunoreactive with at least a portion of a human usherin protein under

conditions effective to produce an immunoconjugate if the usherin protein is present, wherein a complement of a polynucleotide encoding the usherin protein is capable of hybridizing to the polynucleotide represented by SEQ ID NO:3 under highly stringent hybridization conditions; evaluating for the presence or absence of the immunoconjugate; and correlating the presence of the immunoconjugate . . . and the absence of the immunoconjugate." Thus, the method of Group I (claims 1-7 and 15-23) and the method of Group II (claims 8-14) include the same overall method steps and Applicants submit that the claims of Group I and Group II are so interrelated that the inventions as claimed can be readily evaluated without placing an undue burden on the Examiner. Reconsideration and withdrawal of the requirement for restriction between Groups I and II is respectfully requested.

Furthermore, the Applicants submit that restriction between the claims in Group I-IV would place an undue burden on the Applicants by requiring payment of three additional filing fees for examination of the non-elected claims, as well as the added costs associated with prosecuting four applications and maintaining four patents.

Reconsideration and withdrawal of the requirement for restriction is respectfully requested.

Previously Filed Information Disclosure Statement

In reviewing the copy of the Information Disclosure Statements initialed by the Examiner and included with the Office Action mailed January 21, 2004, Applicants note that the Examiner has not considered the publication of Kimberling et al., "Gene mapping of Usher syndrome type IIa: localization of the gene to a 2.1-cM segment on chromosome 1q41," *Am J Hum Genet.* 1995 Jan; *56*(1):216-23. Applicants respectfully request that the Examiner consider this publication and initial the Information Disclosure Statement. To assist the Examiner, a replacement copy of Kimberling et al. is attached herewith as Exhibit A.

Objection to the Claims

The Examiner objected to claim 2. In view of the amendment of claim 2 to correct the recitation "group consisting of," withdrawal of the Examiner's objection to claim 2 is requested.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 1-7 and 15-23 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner asserted that the recitation "or combinations thereof" in the Markush groups of claims 2, 4, 5, and 20 rendered these claims indefinite. Applicants disagree. The second paragraph of 35 U.S.C. requires that the claims particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. This requirement is an objective one, evaluated in the context of whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art (MPEP § 2171). "If the claims read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, section 112 demands no more" *(Credle v. Bond,* 25 F.3d 1566, 30 USPQ 1911 (Fed. Circ. 1994)). Applicants submit that the scope and meaning of the recitation "or combinations thereof" in claims 2, 4, 5, and 20 is clear to one of ordinary skill in the art and claims 2, 4, 5, and 20 are not indefinite under 35 U.S.C. §112, second paragraph.

Specifically, the Examiner asserted that claim 2 was indefinite in the recitation "wherein the biological sample is selected from a group including a portion of testis, ovary, placenta, and combinations thereof" (page 5, Office Action mailed January 21, 2004). The Examiner asserted that, although the Applicants have defined the term "an" as including one or more, the recitation of claim 2 "could be reasonably be interpreted as a sample coming from a single individual" and "[i]t is unclear how an individual would have both testis and ovaries and placenta" (page 5, Office Action mailed January 21, 2004). Applicants disagree. The

specification clearly states that "[u]nless otherwise specified, "a," "an," "the," and "at least one" as used herein, are used interchangeably and mean one or more than one" (page 9, lines 1-2 of the specification). Thus, it is improper for the Examiner to limit claim 2 to a sample derived from only a single individual. Further, Applicants submit that there are situations in which a biological sample could include a combination of material from testis and/or ovaries and/or placenta. For example, this could occur in a biological sample containing pooled material from multiple individuals, a biological sample including a panel of samples from different individuals and/or tissues (for example, Figures 3 and 8 of the instant application show panels containing samples from both testis and ovary), or a biological sample obtained from an individual with a genetic and/or developmental anomaly. Applicants submit that claim 2 is not indefinite and withdrawal of this rejection is requested.

The Examiner asserted that claims 4 and 20 are indefinite in the recitation "wherein the detectable label is selected from the group consisting of radioactive labels, non-radioactive labels, and combinations thereof." Specifically the Examiner asserted that it is "unclear how a label can be both radioactive and non-radioactive." See pages 5-6, Office Action mailed January 21, 2004. First, Applicant note that claim 20 does not include the recitation "wherein the detectable label is selected from the group consisting of radioactive labels, non-radioactive labels, and combinations thereof." Further, Applicants submit that the scope and meaning of the recitation "or combinations thereof" in claim 4 is perfectly clear to one of ordinary skill in the art. The detectable label can be of a radioactive label, a non-radioactive label, or a combination of a radioactive label and a non-radioactive label. One of ordinary skill in the art would understand that such a combination could be, for example, a mixture of a radioactive label and a non-radioactive label or a detectable label that has both a radioactive and a non-radioactive component. Applicants submit that claims 4 and 20 are not indefinite and withdrawal of this rejection is requested.

The Examiner asserted that claim 5 is indefinite in the recitation"wherein the antibody is a monoclonal antibody, a polyclonal antibody, or combinations thereof." Specifically

the Examiner asserted that is unclear how an antibody can be both a monoclonal antibody and a polyclonal antibody. See page 6, Office Action mailed January 21, 2004. Applicants disagree. The specification states that "[t]he term antibody is also intended to encompasses mixtures of more than one antibody reactive with the usherin protein (e.g., a cocktail of different types of monoclonal and/or polyclonal antibodies reactive with the usherin protein)" (page 17, lines 13-15 of the specification). Applicants submit that claim 5 is not indefinite and withdrawal of this rejection is requested.

The Examiner asserted that claims 1 and 15 are indefinite in the recitation "complement." Applicants submit that, in view of the amendments to claims 1 and 15, this rejection of claims 1 and 15 is moot.

In view of the above discussion, Applicants submit that the scope and meaning of claims 1, 2, 4, 5, 15, and 20 is clear to one of ordinary skill in the art. Withdrawal of this rejection of claims 1-7 and 15-23 under 35 U.S.C. §112, second paragraph, is requested.

The 35 U.S.C. §112, First Paragraph, Written Description Rejection

The Examiner rejected claims 1 and 15 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully submit that, in view of the amendments to claims 1 and 15, this rejection is moot.

The 35 U.S.C. §112, First Paragraph, Enablement Rejection

The Examiner rejected claims 1 and 15 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an antibody immunoreactive with SEQ ID NO:1, 2, and 4, does not reasonable provide enablement for an antibody immunoreactive with polypeptides that are less than 100% identical with SEQ ID Nos 1, 2, and 4 and polynucleotides encoding such. Applicants respectfully submit that, in view of the amendments to claims 1 and 15, this rejection is moot.

The 35 U.S.C. §103(a) Rejection

The Examiner rejected claims 1-7 and 15-23 under 35 U.S.C. §103(a) as being unpatentable over Hursting et al. (U.S. Patent No. 5,830,681) in view of Eudy et al. (Eudy et al., *Mutation of a gene encoding a protein with extracellular matrix motifs in usher syndrome type IIa*, 1998, Science, 280:1753-1757). This rejection is respectfully traversed. To establish a *prima facie* case of obviousness, "three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP §§ 706.02(j) and 2143.03). Applicants submit that these three basic criteria are not met in the rejection of claims 1-7 and 15-23 under 35 U.S.C. §103(a) as being unpatentable over Hursting et al. in view of Eudy et al.

Hursting et al. in view of Eudy et al. do not teach all the elements of the claimed invention

Applicants submit that Hursting et al. in view of Eudy et al. do not teach or suggest all of the elements of the methods of claims 1-7 and 15-23. Claims 1-7 and 15-23 are drawn to "[a] method of determining whether an individual has or is at risk for developing Usher syndrome Type IIa, the method comprising . . . correlating the presence of the immunoconjugate with the individual not having Usher syndrome Type IIa, and the absence of the immunoconjugate with the individual having or being at risk for developing Usher syndrome Type IIa." Applicants submit that neither Hursting et al. nor Eudy et al. teach or suggest "correlating the presence of the immunoconjugate with the individual not having Usher syndrome Type IIa, and the absence of the immunoconjugate with the individual having or being at risk for developing Usher syndrome Type IIa." The Examiner asserted that Hursting et al. teach "correlating the presence or absence of the immunoconjugate with a disease," and cited column 7, lines 40-56 of Hursting et al. to support this assertion (page 12, Office action mailed January 21, 2004). Applicants find no such teachings of

correlating the presence or absence of an immunoconjugate with a disease at column 7, lines 40-56 of Hursting et al. Nor do Applicants find such a teaching or suggestion anywhere else in the Hursting et al. patent or anywhere in Eudy et al. Further, Applicants find no teaching or suggestion of "correlating the presence of the immunoconjugate with the individual not having Usher syndrome Type IIa, and the absence of the immunoconjugate with the individual having or being at risk for developing Usher syndrome Type IIa" in either of the Hursting et al. patent or Eudy et al. Thus, Hursting et al. in view of Eudy et al. do not teach or suggest all the elements of the method of claims 1-7 and 15-23.

Requisite motivation is absent

Applicants submit that the requisite motivation to combine the teachings of Hursting et al. in view of Eudy et al. is lacking. The Examiner has provided no statement of the motivation to combine the teachings of Hursting et al. in view of Eudy et al. and Applicants submit that no such motivation can be found in the teachings of Hursting et al. or Eudy et al.

Claims 1-7 and 15-23 are drawn to methods of determining whether an individual has or is at risk for developing Usher syndrome Type IIa, the method including incubating a biological sample with one or more antibodies which are immunoreactive with at least a portion of a human usherin protein having SEQ ID NO:4, evaluating for the presence or absence of an immunoconjugate; and correlating the presence of the immunoconjugate with the individual not having Usher syndrome Type IIa, and the absence of the immunoconjugate with the individual having or being at risk for developing Usher syndrome Type IIa.

Hursting et al. teach antibody based methods for detecting and measuring a prothrombin activation peptide (a peptide released upon the coagulation of blood) and methods to be used in the measurement of thrombin activity (see abstract, col. 1, lines 9-16, and claims 2-5 of Hursting et al.).

Eudy et al. teach the cloning of the human *USH2A* gene, the gene responsible for Usher syndrome type IIa (Eudy et al., page 1753), the sequencing of the contiguous cDNA

sequence of *USH2A* (Eudy et al., page 1754, col. 2), the characterization of three different mutations in Usher type IIa patients (Eudy et al. page 1754, col. 2-3), and the conceptual translation of the USH2A open reading frame to obtain a predicted amino acid sequence (Eudy et al., page 1755, col. 2 and Fig. 4A).

Applicants submit that neither documents provides a suggestion, teaching, or motivation to combine the teachings of the Hursting et al. with the teachings of Eudy et al. to obtain the claimed methods. Combining such documents without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985).

No reasonable expectation of success

As previously discussed, Hursting et al. teach an antibody based assay for the detection of a soluble peptide fragment, the prothrombin activation peptide. Hursting et al. do not teach an antibody based assay for the detection of a protein such as usherin, that is, a large, multidomain protein (page 12, line 5 to page 14, line 27 of the specification) located in the basement membrane (page 7, line 24 of the specification). As previously discussed, Eudy et al. teach the *conceptual*, predicted amino acid sequence of the usherin protein (Eudy et al., page 1755). Eudy et al. do not teach the isolation or production of an actual usherin protein, do not teach the preparation of antibodies to the usherin protein, and do not teach the detection of an usherin protein by any known means. Applicants submit that even if one of ordinary skill in the art were to combine the teachings of Hursting et al. in view of Eudy et al., which Applicants submit one would not have been motivated to do, one of ordinary skill in the art would not have a reasonable expectation of success of determining whether an individual has or is at risk for developing Usher syndrome Type IIa from the combined teachings of Hursting et al. and Eudy et al.

For the reasons set forth above, Applicants submit that the invention of claims 1-7 and 15-23 are not unpatentable obvious over Hursting et al. in view of Eudy et al. Applicants request reconsideration and withdrawal of this rejection of the claims under 35 U.S.C. §103.

Summary

It is respectfully submitted that the pending claims 1-7 and 15-23 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicant's Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 21st day of MAY, 2004, at 3:25pm (Central Time).

By: Sara E. Olson
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